The GDUFA II Pre-ANDA Program for Complex Products

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What I’m Going to Cover

- Introduction to the Pre-ANDA program
- Submitting a meeting request through the Portal
- The Pre-ANDA Process
- The Pre-ANDA Meeting Request and Package
- Program Metrics and Trends
- Tips and Advice

Introduction to the Pre-ANDA Program for Complex Generic Drug Products

The Pre-ANDA Program Goal

- The Pre-ANDA Program was established by GDUFA II
  - To clarify regulatory expectations for prospective applicants early in product development,
  - assist applicants to develop more complete submissions,
  - promote a more efficient and effective ANDA assessment process, and
  - reduce the number of review cycles required to obtain ANDA approval, particularly for Complex Products

Complex Products

COMPLEX…	Example	Example Products
Active ingredients	Peptides, complex mixtures, natural source products	Glatiramer acetate
Formulations	Liposomes, emulsions	Liposomal formulation
Routes of Delivery	Locally acting drugs such as dermatological products and complex ophthalmological products	Acyclovir cream
Dosage Forms	Transdermal systems, extended release injectables	PLGA microspheres
Drug-Device Combinations	Dry powder inhalers, nasal sprays	Mometasone Nasal Spray
Other products	Complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement	Abuse deterrent opioid formulations

Components of the Pre-ANDA Program Under GDUFA II

- Research
- Product Specific Guidances (PSGs)
- Controlled Correspondence
- Meetings for complex products

The Three Meeting Types

- Pre-ANDA meetings accelerate access to generics of complex products through early engagement with the FDA
- Pre-ANDA Product development meetings (PDEV)
  - Early engagement in your individual product development program
- Pre-Submission meetings (PSUB)
  - Ready to or close to submitting your application
- Mid-review-cycle meetings (MRCM)
  - After your ANDA has been submitted

Pre-ANDA Meeting Goal Dates

- Within 30 days (year one and two) or 14 days (year three and beyond) FDA will respond to the request and grant or deny the meeting
- 5 days before the meeting you will receive preliminary written comments from FDA
- If a meeting is granted, FDA will offer a meeting date within 120 calendar days of granting the request
- Meeting minutes will be sent 30 days after the meeting

Product Development Meetings

- A meeting involving a scientific exchange to discuss specific issues or questions
  - A novel proposed study design
  - Alternative bioequivalence approach
  - Additional study expectations
- FDA will provide targeted advice regarding an ongoing ANDA development program

Pre-Submission Meetings

- A meeting to discuss and explain the format and content of an ANDA to be submitted
- Applicants can obtain advice that will enable efficient review and improve the chance of first cycle approval
- Pre-submission meetings will not include substantive review of summary data or full study reports
- ANDA expected to be submitted within 6-12 months

Mid-Review-Cycle Meeting

- Provide the applicant with an update on the status of the review of their application.
- Mid-point plus 30 days
- Dependent on PDEV and PSUB meeting

Pre-ANDA Meeting Decision

- FDA will grant a prospective applicant a Product Development Meeting if, in FDA's judgment:
  - The meeting concerns development of a Complex Product for which FDA has not issued product-specific guidance or proposes an alternative equivalence evaluation (i.e., change in study type, such as in vitro to clinical) for a Complex Product for which FDA has issued product-specific guidance;
  - The prospective applicant submits a complete meeting package, including a data package and specific proposals;
  - A controlled correspondence response would not adequately address the prospective applicant's questions; and
  - A Product Development Meeting would significantly improve ANDA assessment efficiency.

Pre-ANDA Meeting Decisions

- A product development meeting may be granted if the meeting concerns complex product development issues other than those identified above (e.g., FDA has developed a product-specific guidance and the prospective ANDA applicant is not proposing an alternative equivalence evaluation), dependent on available resources, if:
  - The prospective applicant submits a complete meeting package, including a data package and specific proposals,
  - A controlled correspondence response would not adequately address the prospective applicant's questions,
  - A Product Development Meeting would significantly improve ANDA assessment efficiency

Mid-Review-Cycle Meetings

- Occur post-submission
- Only held once via a teleconference during the first review cycle with ANDA applicants that have participated in a prior product development or pre-submission meeting
- Generally take place 30 days after the mid-point of the review cycle
  - After the last key discipline has issued its IR/DRL

IR: Information Request; DRL: Discipline Review Letter

CDER Direct NextGen Collaboration Portal

Submitting a meeting request

What is the Portal?

- Also known as the CDER Direct NextGen Collaboration Portal
  - The portal for short
- The portal website - https://edm.fda.gov

What is the Portal For?

- A website where industry can submit information to the FDA
- Besides pre-ANDA meetings, the portal is used for
  - Drug shortages – to notify FDA about a drug shortage or supply issue
  - Program Fees – To enter GDUFA II program fee information
  - Licensure – to submit an application for a WDD and/or 3PL facility
- Controlled correspondence coming soon

What Should I Use the Portal For?

- Use for pre-ANDA meeting requests for complex generic drug products
  - Previously through the Generic Drugs email account
  - Pre-ANDA product development meetings
  - Pre-submission meetings
- DO NOT USE for mid-review-cycle meetings
  - FDA will contact you if you are eligible

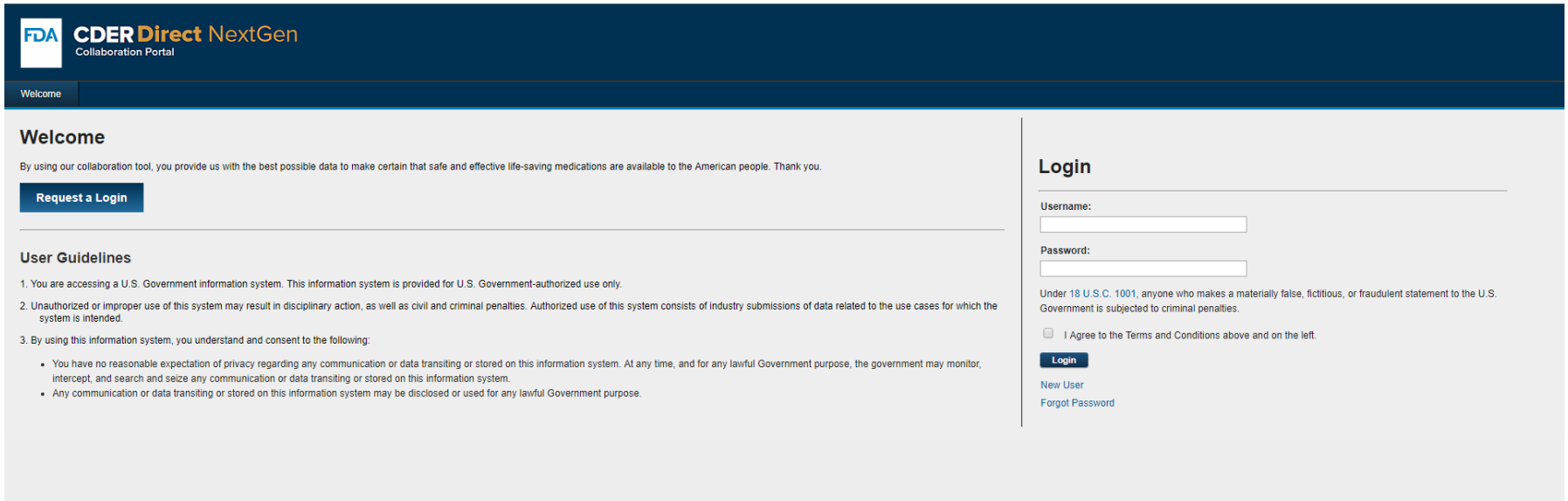
First step: Obtain a pre-assigned ANDA number*

- Apply for a secure email
- You will need a U.S. agent if you are a non-U.S. applicant
- You will need to know your RLD
- Submit an email to cderappnumrequest@fda.hhs.gov with the required information
- Issued within three business days
- Pre-assigned ANDA numbers do not expire

*Requesting a Pre-Assigned Application number

Create a Login for the Portal

- Once on the website, click Request a Login
- Choose Pre-ANDA Meetings as your “event”
- You will register as either a U.S. agent or the applicant
- Enter the required information
- Once approved, you will receive your username and temporary password
- Login request will not be processed until you verify your email


FDA
CDER Direct NextGen
Collaboration Portal
Welcome
Welcome
By using our collaboration tool, you provide us with the best possible data to make certain that safe and effective life-saving medications are available to the American people. Thank you.
Request a Login
User Guidelines
1. You are accessing a U.S. Government information system. This information system is provided for U.S. Government-authorized use only.
2. Unauthorized or improper use of this system may result in disciplinary action, as well as civil and criminal penalties. Authorized use of this system consists of industry submissions of data related to the use cases for which the system is intended.
3. By using this information system, you understand and consent to the following:
• You have no reasonable expectation of privacy regarding any communication or data transiting or stored on this information system. At any time, and for any lawful Government purpose, the government may monitor, intercept, and search and seize any communication or data transiting or stored on this information system.
• Any communication or data transiting or stored on this information system may be disclosed or used for any lawful Government purpose.
Login
Username:
Password:
Under 18 U.S.C. 1001, anyone who makes a materially false, fictitious, or fraudulent statement to the U.S. Government is subjected to criminal penalties.
I Agree to the Terms and Conditions above and on the left.
Login
New User
Forgot Password

Login FAQs

- My organization doesn’t appear when I search
  - You can enter it manually
- I don’t have a DUNS number or I don’t know what it is
  - Use the 9-digit code, 999999999
- Contact the EDM support team if needed at EDMSupport@fda.hhs.gov

My Login has been Created – Now What?

- Click “Create New Request”
- Enter required information
  - Pre-assignment number
  - What type of meeting request are you submitting
  - The Reference Listed Drug (RLD)

Finding Your RLD

- When choosing your RLD, if you notice an error, you have the ability to report a discrepancy through the portal
  - Referencing Approved Products in ANDA Submissions – Guidance for Industry
- If you are unable to find your RLD, email PreANDAhelp@fda.hhs.gov

U.S. Agents

- If you are submitting as a U.S. agent, fill in your applicant's information
  - Search for applicant information or enter manually
  - Provide the applicant contact information
- If you are the applicant, with no U.S. agent, proceed to "Attach a Document"
  - Do not enter yourself as a U.S. agent

Adding Your Documents

- You must add a meeting package in order to proceed
- You can add more than one document
  - Cover letter
  - Meeting package (due at time of request for a meeting)
- Multiple formats allowed
  - PDF, Microsoft Word, Microsoft Excel, Microsoft PowerPoint, Microsoft Access, SAS, and Text. Macros are not allowed. Files may not exceed 45 MB

Submitting Your Meeting Request

- Before you submit your request
  - You have the option of saving your draft meeting request
  - Come back to it later and continue where you left off
  - FDA cannot see saved meeting requests
- You can delete a meeting request if you have not yet submitted it
- You will be asked to review for accuracy
- Click “Submit to FDA”
- You will receive a confirmation message and email once you have submitted your request

Two-Way Communication

- Submit and receive documents through the portal with email notification
- Advantage - All your documents and correspondence in one place

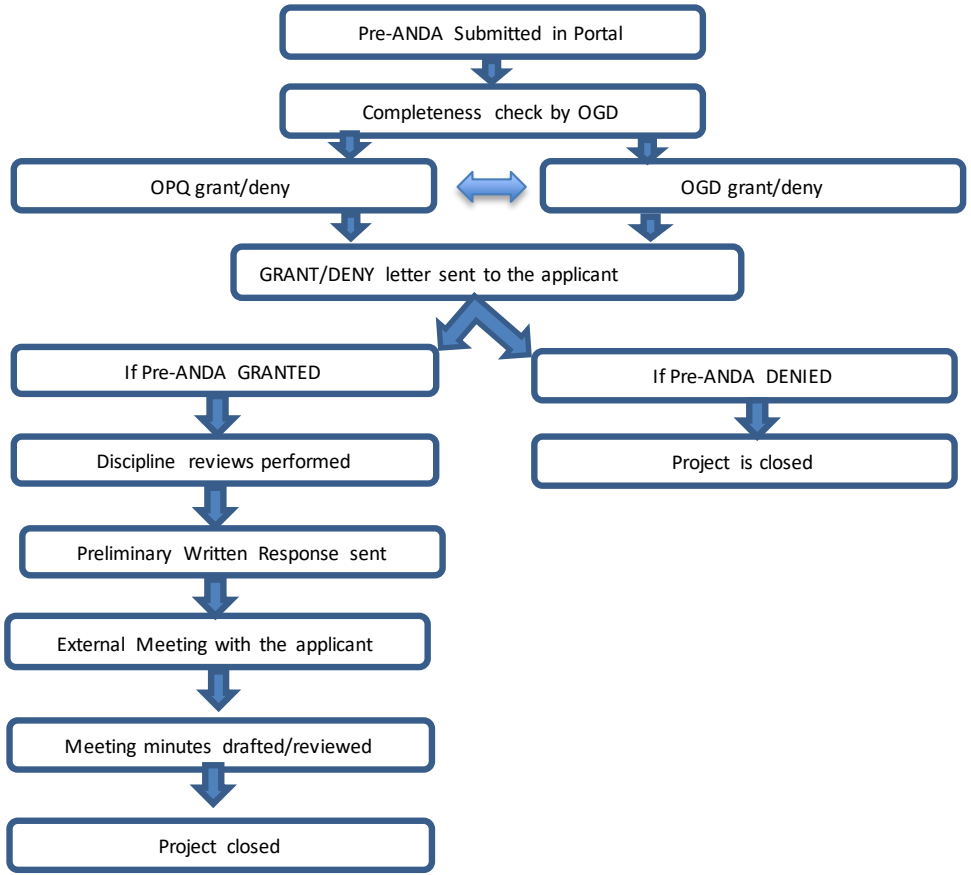
Document Type	File Name	Communication Interaction	Submission Date (EST)	Document Status
Meeting Minutes	ANDA-123465-PDEV-Meeting-00914_Meeting Minutes.PDF	FDA Communication	05/25/2018, 03:39 PM	Reviewed
Post-Meeting Comments	07 - MR Post Meeting Comments.docx	Submitted to FDA	05/25/2018, 03:32 PM	Submitted Document
Response to Information Request	04 - MR Response to IR.docx	Submitted to FDA	05/25/2018, 03:31 PM	Submitted Document
Meeting Presentation Materials	03 - MR Presentation Material.pptx	Submitted to FDA	05/25/2018, 03:30 PM	Submitted Document
Information Request	ANDA-123465-PDEV-Meeting-00914_Send IR.PDF	FDA Communication	05/25/2018, 03:28 PM	Not Reviewed
Preliminary Response to Meeting Questions	ANDA-123465-PDEV-Meeting-00914_Preliminary Response to Meeting Questions.PDF	FDA Communication	05/25/2018, 03:18 PM	Not Reviewed
Meeting Scheduled Information Letter	ANDA-123465-PDEV-Meeting-00914_Send Meeting Scheduled Letter.PDF	FDA Communication	05/25/2018, 03:14 PM	Not Reviewed
Meeting Grant Letter	ANDA-123465-PDEV-Meeting-00914_Meeting Grant or Deny Letter (or Withdrawn-Canceled Letter).PDF	FDA Communication	05/25/2018, 02:55 PM	Not Reviewed
Meeting Request Package	02 - MR Package.pdf	Submitted to FDA	05/25/2018, 12:14 PM	Submitted Document

If You Need Help

- There are several help guides and tutorials on the Learn More page for reference
- For portal support, contact EDMSupport@fda.hhs.gov
- For meeting specific help contact PreANDAHelp@fda.hhs.gov

The Pre-ANDA Meeting Process

Pre-ANDA PROGRAM OUTLINE



Phase 1 (30 days)

Phase 2 (120 days)

Phase 3 (30 days)

What Happens First?

- Administrative review
  - Verify pre-assignment number
  - Is there a meeting package with questions

Meeting Request Evaluation

- Assessment team will evaluate Pre-ANDA meeting requests
  - OGD and OPQ perform separate triage functions to determine grant/deny and the extent of participation
  - OGD and OPQ coordinate to provide a unified response
  - The assessment team reviews the product details, contents and submitted questions in the meeting package
  - The assessment team determines whether the meeting is granted or denied

Grant/Deny Assessment

- Within 30 days (year one and two) or 14 days (year three and beyond) FDA will respond to the request and grant or deny the meeting
- If a meeting is denied, FDA will provide information to the applicant on a path forward
- If a meeting is granted, FDA will offer a meeting date within 120 calendar days of granting the request

FDA Staff Roles (OGD)

- Division Level Signatory
  - An ORS division director or deputy who makes the decision to grant and oversees the meeting process
  - Accountable for the accuracy and completeness of FDA's response
- Meeting Project Manager
  - Point of contact for industry
  - Facilitates internal meeting preparation, consults and information sharing
- Meeting Team Leader
  - Responsible for coordinating all discipline reviews into a consistent response

FDA Staff Roles (OPQ)

- OPQ Triage Team
  - An OPQ team that is responsible for determining grant/deny for meeting requests and the extent of OPQ participation, if any
  - Responsible for assigning OPQ disciplines to meeting package review

- OPQ Disciplines
  - Drug substance, drug product, process and facilities, microbiology, biopharmaceutics, research
  - Responsible for answering discipline-specific questions

- OPQ Meeting Team Leader
  - Responsible for coordinating all OPQ discipline reviews into a consistent response

What Happens Next?

- A letter with the grant or deny decision will be sent to you through the portal
- A meeting denied letter will complete your project
  - You will be advised on the next steps, for example, submit a controlled correspondence instead

My Meeting Was Granted

- Typically granted as face-to face meeting, though the applicant can request a written response or teleconference
- Written responses and t-cons still qualify you for a mid-review-cycle meeting
- Information Requests (IR)
  - Sent to the applicant through the portal
  - Can be sent to the applicant at any time
  - FDA strives to send early in the process
  - Applicant responds to the IR through the portal

Meeting Package Review

- Discipline reviews performed based on meeting package questions
  - Not all disciplines for all pre-ANDA meetings
- Responses are based upon the agencies current thinking and knowledge
  - May change with available data or research, etc.
- OGD compiles the preliminary response with input from all involved disciplines

Preliminary Responses

- Preliminary responses for face-to-face meetings and teleconferences will be sent through the portal approximately five days before your scheduled meeting
- Your opportunity to focus your meeting for clarification
  - Submit presentation materials (not required)
  - Submit a revised agenda
  - Submit these through the portal

  Do not submit until after you have received your preliminary response
- You can cancel your meeting if you feel the preliminary responses adequately address your questions – you will still be eligible for a MRCM if you cancel your meeting after you have received the preliminary response

Meeting Day

- Prospective ANDA applicant submits meeting slides and agenda via the Portal approximately 48 hours before
  - Meetings are typically one hour
  - Agenda should be focused on clarification or further discussion around the preliminary written comments

- Meeting participants discuss the data, questions and the responses provided to assist the prospective ANDA applicant's complex product development program

- **FDA cannot review new material presented at the meeting for the first time**

After the Meeting

- The applicant can submit post meeting comments through the portal
  - Within seven days of the meeting
- FDA will send the final meeting minutes through the portal within 30 days of the meeting
- This completes the meeting request

Pre-ANDA Continuity

- For pre-submission meetings, FDA will identify representatives of the ANDA review team to participate in the meeting

- For pre-submission meetings and subsequent ANDA submissions, FDA will communicate the results of the product development meeting or other pre-ANDA interactions to the review team

- Meetings are automatically pulled into the ANDA program once the ANDA is submitted using the pre-assigned ANDA number associated with the meeting request
  - Using the pre-assigned ANDA number for controlled correspondence will also aid this linkage

The Pre-ANDA Meeting Package

Meeting Package Format

- Refer to the draft guidance (Oct 2017)
  - Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA Guidance for Industry
- Number your questions clearly and group them by discipline
  - e.g., Bioequivalence, CMC, etc.
- Minimize the use of sub questions, for example a, b, c, etc.

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm578366.pdf

Meeting Package Content: Product Development Meetings

- Provide clear and specific questions about your development program

- Include data supporting the proposed new approach that may include
  - Characterization of the RLD and ANDA products
  - Results from pilot studies
  - Comparisons of the proposed approach to that currently recommended by FDA
  - Quantitative analysis (PBPK, PK/PD, or BE simulation) that supports your approach

Meeting Package Content: Pre-Submission Meetings

- Outline the unique, novel or complex aspects of your upcoming submission that you will present at the meeting

- If you have specific questions, provide appropriate background material and data related to those questions

Meeting Package Review

- A project manager from the Office of Research and Standards (ORS) is assigned as a point of contact
- FDA staff will review the meeting package, request consults and send information requests (if needed)
  - Prospective ANDA Applicant responds to any IRs via the Portal
- FDA will strive to send preliminary written responses five days prior to the meeting

Program Metrics and Trends

GDUFA II Pre-ANDA Metrics*

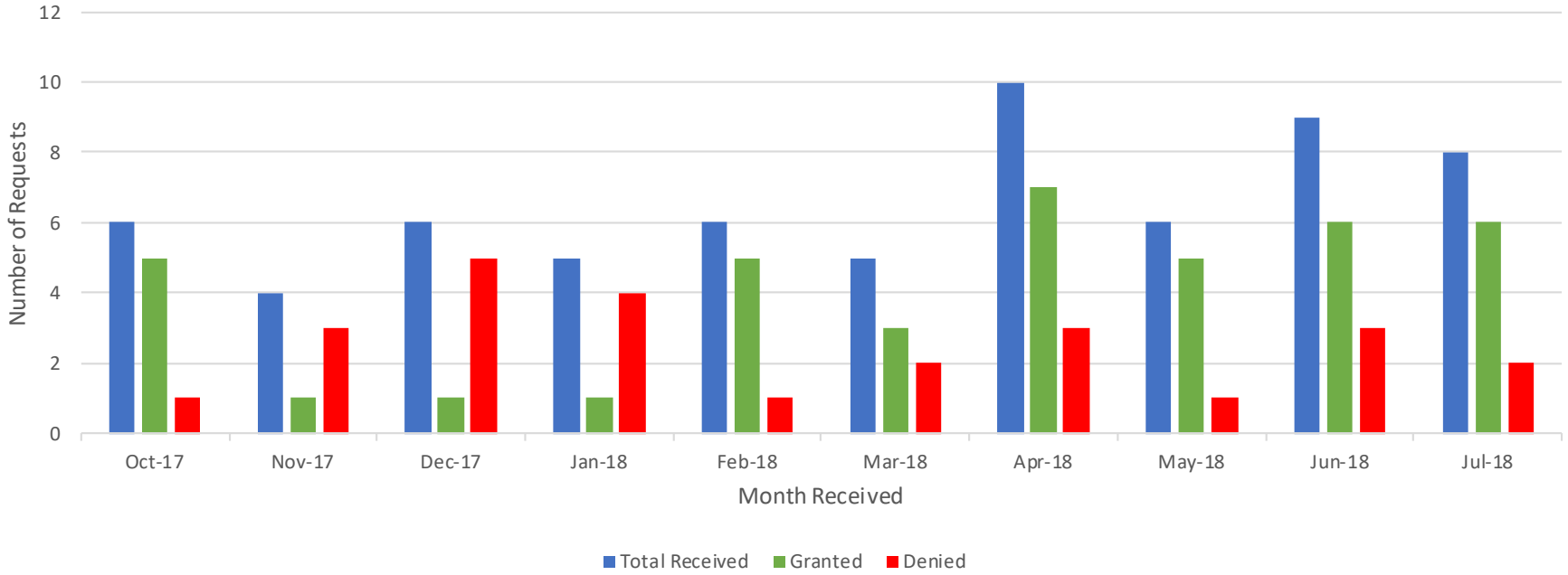
- Ten months into the program, 65 pre-ANDA meeting requests have been submitted
- 40 have been granted, 25 denied
  - Denied meetings are given a path forward, such as re-submit as a control or re-submit your meeting request with the following information (inadequate meeting package)

*Data as of 7/31/2018

Most Common Types of Products

- Topicals
- Ophthalmics
- Inhalation
- Injectables (complex)

Granted vs Denied



Common Reasons for Denial

- Incomplete meeting packages
- Not a complex product
- Wrong meeting type chosen – PDEV vs PSUB
- Should be a controlled correspondence
- PSG is available and not asking for an alternate bioequivalence route

Tips and Advice

Tips Based on What We've Seen So Far

- Provide sufficient data to review question in the meeting package
- Q1/Q2 questions where not required by regulation or recommended in a PSG—yes this is the pathway
  - Submit a meeting request that proposes a BE approach for a specific formulation
  - FDA will provide feedback on the BE approach
  - If you know you are not Q1/Q2, include your justification

Submitting Devices

- Read the guidance on Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA
  - Posted in January 2017
  - AKA: Comparative Analyses Guidance
- Consider when and how to submit your device
  - As part of a meeting request or as a control?
  - Prototype or final design?
  - What about 3D printed devices?

Am I a Pre-sub or Prod-dev Meeting?

- Product Development meetings are for discussion of specific scientific issues
  - Proposed study design, alternative approach, additional study expectations

- Pre-submission meetings are for 6-12 months before submission
  - You are ready to submit
    - Do you have your stability batches started?
  - Discuss format and content of ANDA
    - Not a filing review

Am I a Controlled Correspondence or Prod-Dev?

- Standard controls reviewed in 60 days
  - Use for guidance clarification and rapid input into development programs
- Complex controls reviewed in 120 days (new in GDUFA II)
  - Clinical input (protocols for Safety determination letters)
  - Alternate BE approach (within the same class)
- Complex control expands what we can consider via the control process
- Clarification of ambiguities are allowed – see Controlled Correspondence Related to Generic Drug Development Guidance for Industry

Optional Meeting or Control?

- Meetings are best for multidisciplinary questions
- Controls are for single questions or a small group of closely related questions
- Consider timelines – how soon will I get my answer?

Examples of useful questions

- Do not submit a protocol and ask us to review it
  - Instead submit specific questions regarding your protocol
- What tests should I do?
  - Instead propose your development plan with appropriate justification

Examples of useful questions

- Is my PK study acceptable?
  - Instead identify the point of uncertainty and ask a specific question
- Is my specification acceptable?
  - Instead ask a specific question about this complex product and your understanding of how you will control the CQA of your product

Take-Aways

- Use the portal to submit your meeting requests
- Read the guidance
  - "Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA"
- Choose the correct pathway
  - Product Development, Pre-submission, or Controlled Correspondence
- Provide sufficient information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